REMARKS AND ARGUMENTS

Amendments to the Specification and Abstract

The Examiner has requested that Applicants amend the title, stating that the title is not descriptive of the elected claims. However, since prosecution of the claims is ongoing, Applicants wish to defer amendment of the title until the claims have been allowed.

The specification is amended herein primarily to correct a number of misspelled words. Since there are approximately 40 paragraphs of the specification being corrected, in accord with 37 C.F.R. § 121(b)(3) a redlined version, as well as a clean copy of the full specification, is being provided in lieu of setting out each corrected paragraph separately. In addition, the Abstract of the Disclosure has been revised to remove unnecessary wording. Please replace the originally submitted specification with the enclosed substitute specification, including the rewritten Abstract. The substitute specification contains no new matter. Applicants have amended the specification to correct several obviously misspelled words and other minor errors as indicated in the enclosed redlined substitute specification. Correction of misspelled words does not constitute the addition of new matter to the application.

In the paragraph beginning at page 82, line 11 of the originally submitted specification, the text stating "Table 3 below" was changed to "Table 5 below." Since Table 3 appears on page 78, it is self-evident that "Table 3" is incorrect. The only table appearing "below" page 82, line 11 is the table at page 83. This table clearly should have been labelled "Table 5," as a "Table 4" appears at page 81. Accordingly, the number of this table has been corrected as well as the text referring to the table. Thus, the amendments relating to this table do not constitute the addition of new matter to the application.

In the paragraph beginning at page 15, line 26 of the original application and also in the paragraph beginning at page 40, line 35 of this same document, another error was corrected as set forth below. This inadvertent error appeared in the sentence shown below with the amendments included (this sentence begins at page 15, line 33 of the original specification):

> "Such 4-1BB antagonists include,...antibodies, fusion proteins and/or peptibodies directed against 4-1BB that specifically bind 4-1BB and partially or completely inhibit binding of 4-1BB to 4-1BB-L; antibodies, ~~fuion~~ fusion proteins and/or peptibodies directed against ~~4-1BB~~ 4-1BB-L that specifically bind ~~4-1BB~~ 4-1BB-L and inhibit binding of ~~4-1BB-L~~ 4-1BB without themselves transducing a signal via ~~4-1BB~~ 4-1BB-L..."

Unless amended, the above sentence would contain two sequential phrases that both describe antibodies, peptibodies and fusion proteins against the same target. It would be self-evident to a reader that the duplication of this phrase must have been unintended. The reader

would surmise that either one of the phrases was not meant to be there at all, or that the target specified in the second of the two phrases was meant to differ from the target specified in the first. In view of the application taken as a whole, it would be self-evident that the latter is the case.

It is clear from the disclosure that the 4-1BB antagonists of the invention include both antibodies against 4-1BB and antibodies against 4-1BB-L. Accordingly, it would be self-evident that the first iteration of the above-discussed phrase was meant to recite antibodies to 4-1BB, and the second iteration was meant to recite antibodies to 4-1BB-L. Applicants respectfully submit that this conclusion is obvious in light of several statements found throughout the specification. One such example is the second sentence of the paragraph containing the sentence quoted above. This sentence states: "[i]n other words, because the 4-1BB:4-1BB-L interaction exhibits bi-directional signalling, *a 4-1BB antagonist may bind either 4-1BB or 4-1BB-L* so long as the antagonist does not itself activate 4-1BB or 4-1BB-L." (page 15, lines 30-33 of original application, emphasis added). This statement is entirely consistent with the amended sentence shown above.

In addition, the specification states also at page 5, lines 24-27 of the originally submitted specification that "[a]ntagonists presented herein further comprise *antibodies, fusion proteins and peptibodies directed against one or more of the following*: IL-17, IL-17R, IL-18, IL-18R, CD30, CD30-L, *4-1BB, 4-1BB-L*, OX40 and/or OX40-L." (emphasis added)

Moreover, at page 40, line 34 the specification states that "IL-17, IL-18, *4-1BB*, CD30 and OX40 *antagonists include antibodies that specifically bind* IL-17, IL-17R, IL-18, IL-18R, IL-18BP, *4-1BB, 4-1BB-L*, CD30, CD30-L, OX40 or OX40-L." (emphasis added).

Numerous other examples of such disclosure exist throughout the specification. In view of these disclosures, the amendments discussed above do not constitute the addition of new matter to the application. Applicants note that the same reasoning applies to the similar proposed amendment to the paragraph beginning at page 40, line 35 of the original specification.

In addition, on page 16, lines 19, 20, 22, 24, 25, and 27 of the original specification, the specification has been amended to correct the SEQ ID numbers of 4-1BB-L cDNA to SEQ ID NO:15 from SEQ ID NO: 14, and the amino acid sequence of 4-IBB-L to SEQ ID NO:16 from SEQ ID NO:15. These SEQ ID NOs are correctly stated in the specification as originally filed, for example, page 17, lines 13-15, and lines 27-29. In addition, it is clear from the sequence listing as filed with the application that SEQ ID NO: 15 is a nucleic acid sequence and SEQ ID NO: 16 is the protein sequence of 4-1BB-L. Therefore, the amendment on page 16 does not constitute the addition of new matter into the specification.

Lastly, the Abstract of the Disclosure has been rewritten as shown in the redlined version of the substitute specification. The Abstract was revised to remove the last sentence

of the abstract, and other additional wording as unnecessary. The amendment to the Abstract does not constitute the addition of new matter to the application. Entry of the amendments to the specification including the abstract is respectfully requested.

Amendments to the Claims

Claims 31 to 53 and 55 to 67 are currently pending in the application. Claims 31-45, 53, and 55-62 are withdrawn in response to the restriction requirement or election of species. Claim 54 has been canceled without prejudice to future filing. Claims 46 to 52 and 63 to 67 are currently undergoing prosecution. Claims 46 to 48, and 50 to 51 are amended. Claim 46 is amended to recite "*preventing or* reducing chronic cardiotoxicity", thereby more clearly reciting the subject matter considered to be the invention. Basis for this amendment is found in the specification, for example, page 67, lines 3 to 21, of the specification as originally filed. Claims 47 and 48 have been amended to recite cardiomyopathy and antracycline drug respectively in response to the restriction requirement. Claim 50 has been amended to recite a soluble 4-1BB protein and antibodies that "blocks *or reduces* the interaction of 4-1BB and 4-1BB-L". Basis for the amendment is found in the specification, for example, page 15 of the originally filed specification, lines 26 to page 16, line 3. Claim 51 is amended to recite a soluble 4-1BB *protein*, as is recited in claim 50. No new matter is presented by the amendments to the claims, and entry of the amendments to the claims is respectfully requested.

Claims 63 to 67 have been added. Basis for claim 64 is found in the specification as originally filed, for example, page 34, line 15 to page 37, line 10, describing a number of forms of oligomers. Basis for claims 65 to 67 is found in the specification, for example, page 17, lines 8-12 of the specification as originally filed. Therefore added claims 63 to 67 do not present new matter, and entry of claims 63 to 67 is respectfully requested.

Rejections on the Basis of 35 U.S.C. § 112

Claims 46-49, 52 and 54 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter that was not described in the application. This rejection is respectfully traversed.

The Examiner has alleged that the specification describes only three types of antagonists, a soluble 4-1BB, an antibody to 4-1BB and an antibody to 4-1BB-L. While Applicants do agree that these three antagonists are taught in the specification, Applicants do not agree that these are the only three types of antagonists described in the specification. The specification as filed further describes, for example, a soluble 4-1BB-L, such as a polypeptide comprising amino acids 49 to 254 of SEQ ID NO: 16 (page 17), polypeptide mimetics, such as peptidomimetics based on SEQ ID NO: 18 (4-1BB) and SEQ ID NO: 16 (4-1BB-L) (page 17), muteins (page 27) and variants including PEGylated peptides (page 33), oligomeric forms of 4-1BB (pages 34-37), and antisense RNA and DNA molecules (pages 44-47). Clearly multiple forms of antagonists are described in the specification. Furthermore, Applicants point to Example 7, pages 77 to 79, of the specification. The experiments in Example 7 are done with 4-1BB-L knockout mice, and demonstrated that the knockouts showed no mortality and delayed onset of cardiac dysfunction in an Adriamycin® induced model of cardiomyopathy. Thus Example 7 demonstrates the relationship between antagonizing 4-1BB and reducing chronic cardiotoxicity caused by a chemotherapeutic agent in a subject, without limitation to a particular antagonist. Therefore, Applicants submit that the method as recited in claim 46 does not need to be restricted to a particular antagonist.

On the basis of the remarks set forth herein, and the amendments set forth above, Applicants request reconsideration and withdrawal of the rejection of claims 46-49, 52 and 54 on the basis of 35 U.S.C.§112, first paragraph.

Claim 54 has been rejected under 35 U.S.C. §112, first paragraph, as lacking enablement, and under 35 U.S.C. §112, second paragraph, as indefinite for allegedly failing to particularly point out and distinctly claim the subject matter considered to be the invention. These rejections are respectfully traversed. Claim 54 has been canceled and therefore, these rejections are considered to be moot.

Rejections under 35 U.S.C. § 103(a)

Claims 46-52 are rejected under 35 U.S.C.§103(a) as allegedly unpatentable over the publication of Yndestad et al., and U.S. Patent 5,674,704 to Goodwin et al., in view of Waelti U.S. published application 2004/0028687. This rejection is respectfully traversed.

103(a) states in part that "A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the difference between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains."

First, Applicants do not agree that the difference between the claimed subject matter, and what is published in the reference to Yndestad et al., in combination with the issued patent to Goodwin et al., and in view of the published patent application to Waelti, would have been obvious to one of ordinary skill in the art. The claimed invention is directed to a method of preventing or reducing chronic cardiotoxicity caused by a chemotherapeutic agent in a subject comprising administering to the subject a 4-1BB antagonist in an amount sufficient to reduce the cardiotoxicity.

Yndestad et al. describes increased gene expression of a large number of cytokines, receptors, orphan receptors, TGFß superfamily members and TNF superfamily members (Table 3) in chronic heart failure patients. As stated in the abstract, "From 375 genes, 34 were upregulated, and two downregulated in CHF patients in the cDNA expression array experiments." (abstract, page 175). The Examiner has quoted page 176 of Yndestad et al. "there is strong evidence for TNF as a pathological factor in CHF, other members of the TNF superfamily may *potentially* be even more important" (page 6 of Office Action, quoting Yndestad, page 176, emphasis added). However, on page 181 (4.4, Conclusion paragraph), Yndestad et al. also provides evidence that antagonizing TNF does not actually work in vivo, for example, soluble TNF-R did not reduce IL-6 levels in myocardium in animal studies, and that entanercept, a soluble TNF-type 2 molecule, failed to be efficacious in two clinical trials.

In addition, there is nothing in the reference to Yndestad et al. to indicate to one of ordinary skill in the art that 4-1BB in particular would be the "obvious" target for therapeutic antagonists from among all of the other molecules identified. On the contrary, 4-1BB would appear to be the least likely target from the results shown in this reference. The TNF superfamily ligands studied include 7 that were upregulated and one that was downregulated. (Table 3, page 178). In the discussion on page 180, paragraph 4.3, Yndestad et al. points out that "receptors of APRIL, FasL, LIGHT, TNFα and TRAIL", (but *not* 4-1BB), "have been reported to be expressed in the heart", and these may be involved in potential pathogenic pathways (page 180, section 4.3). Further, the discussion continues that "abnormal apoptosis is recognized as a potential pathogenic factor in myocardial failure and known death-inducing

ligands such as TNFα, FasL, TRAIL, and LIGHT," (but *not* 4-1BB-L) "that all were upregulated in CHF patients in the present study, may well be involved in this process". (section 4.3, pages 180-181). Instead, it was the instant application that identified that 4-1BB may increase Adriamycin®- related heart damage through apoptosis (Example 8.2, pages 80-81).

Further, on pages 179 to 180, Yndestad et al. states that real-time quantitative RT-PCR experiments confirmed the upregulation of four of the six ligands, APRIL, CD27L, FasL, and LIGHT, however, "the upregulation of 4-1BBL and CD40L were not verified" (page 180) using this second technique. Therefore, for these three reasons, this publication might possibly prompt investigation of APRIL, FasL, LIGHT, TNFα, TRAIL, CD27L, but *not* 4-1BB.

Further, there was no discussion in the publication of Yndestad et al. of preventing or reducing chronic cardiotoxicity due to a chemotherapeutic agent, and there is nothing in this publication to suggest that antagonizing 4-1BB alone would prevent or reduce cardiotoxicity due to chemotherapeutic treatment. 4-1BB was not known to be expressed in the heart, according to this paper. The upregulation of 4-1BB-L found in cDNA arrays could not be confirmed by RT-PCR according to this paper. 4-1BB-L was not known to produce apoptosis of cardiac cells, according to this paper.

Futher U.S. Patent 5,674,704 describes 4-1BB and 4-1BB-L DNA and protein including soluble protein. There is no description or suggestion of antagonizing 4-1BB to treat chronic cardiotoxicity or cardiomyopathy in this reference. These two references appear to be completely unrelated. Finally, the reference to Waelti et al. mentions that anthracycline anticancer compounds have certain side effects including dose-dependent cardiotoxicity [0022]. Waelti et al. does not mention 4-1BB or 4-1BB-L nor provide any suggestion that antagonizing 4-1BB would prevent or reduce cardiotoxicity. Therefore, it would not be *obvious* to one of ordinary skill in the art, based on Yndestad et al. and Goodwin et al., in view of Waelti et al., that antagonizing 4-1BB alone would prevent or reduce cardiotoxicity caused by a chemotherapeutic agent. Applicants submit that, for the reasons set forth above, a *prima facie* case of obviousness has not been made by the Examiner.

Therefore, Applicants submit that the combination of these three references does not render the claimed invention obvious, and request reconsideration and withdrawal of the rejection of claims 46-52 on the basis of 35 U.S.C. § 103 (a).

Applicants' attorney invites the Examiner to call her at the number given below if it would be helpful in advancing the prosecution of this application.

Respectfully submitted,

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